Kindly amend the application as follows[1]:

IN THE SPECIFICATION

Replace the title on page 1 with the following phrase:

HUMAN K^+ ION EAG CHANNELS

Replace the paragraph on page 9, line 22 to page 10, line 18 with the following:

Due to the prior art failures to clone human *eag* gene from brain libraries and the above recited uncertainties with immortalized cell lines, another source for a library was in need. The 400 bp fragment was therefore used to screen a normal human breast cDNA library. Due to the presence of *eag* is breast cancer cells, such a library was expected to comprise h*eag* clones. Surprisingly, however, after screening 2x 10^6 phages, no human-*eag* clones could be identified in said library. This rises the possibility that the channel is expressed only in tumor cells, and not in normal tissue. Specific oligonucleotides, namely 5'-CCAAACACACACACCAGC (SEQ ID NO: 5) and 5'-CGTGGATGTTATCTTTTTGG (SEQ ID NO: 6), were designed to check for h*eag* fragments by PCR amplification directly from the above library, but no evidence for the presence of any *eag* clones in this library was found. In view of the above discussed prior art results, it came as a further surprise that the

[1] An "Appendix of Amendments" is enclosed showing the amendments to the Title, Specification and the claims. In the Appendix, the added portions are underscored and the deleted portions are bracketed.

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same primers detected h*eag* in a normal human brain cDNA library, that was therefore screened. First, the probe obtained from MCF7 cells was used to check 10^6 phages. This procedure allowed to isolate a 1.6 kbp fragment from human *eag*. This fragment was then used as a probe for the screening of $2x10^6$ phages from the same library. Several independent clones were isolated, but none of them was a full-length clone. Furthermore, only one clone contained the 5' end of the sequence, while two of them contained the 3' end and part of the 3' non-coding region. It is likely that the abundance of restriction sites in the nucleic acid sequence encoding the channel has induced this extensive fragmentation of the cDNA. For example, when EcoRI was used to extract the inserts of the library that was cloned in λ-gt10 phage at the EcoRI site, this conventional approach systematically failed to find the 5' end of the molecule (there is an EcoRI site at position 400 of the clone). The pooled positive clones were therefore screened again by PCR, trying to amplify the start codon, and only by this means was it possible to isolate one phage that contained this ATG. Two splice variants of h*eag* were cloned, both expressed in brain tissue. The sequences obtained for h*eag* 1 and h*eag* 2 and their deduced amino acid sequences are shown in Figures 10 and 11, and compared to other members of the family.

C1 Cont

Replace the paragraph on page 11, lines 15–17 with the following:

The present invention also relates to a nucleic acid molecule specifically hybridizing to the nucleic acid molecule of the invention which comprises the sequence 5'-GGGAGGATGACCACATGGCT (SEQ ID NO: 7).

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Replace the paragraph on page 30, lines 18–20 with the following:

Figure 10. Nucleotide sequence of human-*eag* cDNA (heag; SEQ ID NO: 1) from human brain compared to the rat sequence (reag; SEQ ID NO: 20) and bovine sequence (beag; SEQ ID NO: 19). Those positions showing a different nucleotide in any of the sequences are shaded.

C3

Replace the paragraph on page 30, lines 21–23 with the following:

Figure 11. Amino acid sequences of both splice variants (heag1 (SEQ ID NO: 3) and heag2 (SEQ ID NO: 4)) obtained from human *eag* cDNA translation, compared to the corresponding bovine (beag1; SEQ ID NO: 21; beag2; SEQ ID NO: 22), mouse (meag; SEQ ID NO: 23) and rat (reag; SEQ ID NO: 24) sequences. The black boxes indicate a different residue in any of the sequences.

C4

Replace the paragraph on page 33, lines 15–17 with the following:

The sequences of the oligonucleotides were the following:

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5'-CAGAA(T,C)AA(T,C)GTGGC(A,C,T,G,)TGGCT (SEQ ID NO: 8).

5'-TCACT(G,A)AAGATCTATA(A,G)TC (SEQ ID NO: 9).

Replace the paragraph on 36, line 24 to page 37, line 8 with the following paragraph:

500 ng total RNA from different tissues (or 5 ng polyA$^+$ RNA, for spinal cord) were reverse transcribed and amplified using a pair of oligonucleotides of the sequences, 5'-CGCATGAACTACCTGAAGACG (SEQ ID NO: 10) (forward) and 5'-TCTGTGGATGGGGCGATGTTC (SEQ ID NO: 11) (reverse). The amplified DNA was analyzed by Southern blot using a specific human *eag* probes (a 1.5 kb EcoRI fragment from the core of the channel). Among the RNAs tested, only brain total RNA gave positive signals. RNAs from spinal cord, adrenal gland, skeletal muscle, heart trachea, liver, kidney and mammary gland were negative. The integrity of the RNA was checked using transferrin amplification. Using the same approach, the expression of h*eag* in several tumoral human cell lines was checked, in: MCF-7 (breast adenocarinoma), BT-474 (breast ductal carcinoma, from a solid tumor), EFM-19 (breast carcinoma, ductal type, from pleural fluid), COLO-824 (breast carcinoma, ductal type, from pleural fluid), SHSY5Y (neuroblastoma).

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Replace the paragraph on page, 37 lines 11–30 with the following paragraph:

Further, Southern blot of RT-PCR products of RNAs from different human tissues and 293 cells show that only in RNA from brain the two bands corresponding to h*eag* A and B could be amplified and identified. Transferrin receptor (TFR) signals are shown at the bottom (Fig. 15A). Furthermore, a Southern blot analysis of RT-PCR products of total RNAs from different human cell lines an mammary epithelial cells in primary culture (Epith.

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cells). TRF signals are shown at the bottom. RNAs from different cell lines (34) and commercial RNAs from human tissues (Clontech) were subjected to single-tube RT-PCR (35). Total RNA was used with the exception of spinal cord, where poly(A)$^+$ RNA was used (primer sequences were: forward: 5'-CGCATGAACTACCTGAAGACG (SEQ ID NO: 10) and reverse: 5'-TCTGTGGATGGGGCGATGTTC (SEQ ID NO: 11). 5'-TCAGCCCAGCAGAAGCATTAT (SEQ ID NO: 17) and reverse: 5'-CTGGCAGCGTGTGAGAGC (SEQ ID NO: 18) were used to control RNA and PCR performance.). Specific primers for TFR were used to control RNA and PCR performance. These ODNs were designed according to the published TFR sequence (36), starting at exon 11 and spanning to exon 19 (37). This, together with the amplification of two h*eag* splice fragments and controls in the absence of reverse transcriptase, excludes a false positive due to genomic DNA contamination. 50 µl (h*eag*) or 15 µl (TFR) of PCR reactions were analyzed in 2% agarose gels. DNA was transferred to membranes and consecutively hybridized at high stringency with [^{32}P]-dCTP labeled random primed probes consisting of a 980 bp h*eag* fragment and the TFR fragment amplified from brain RNA.

C7 Cont

Replace the paragraph on page 39, lines 6–15 with the following paragraph:

It is assumed that expression of h*eag* in some tumor cells is not the consequence of their abnormal growth, but that this K^+ channel is necessary for their proliferation. Therefore, inhibition of h*eag* expression with antisense oligodeoxynucleotides (ODNs) should decrease the proliferation rate in these tumor cells. Therefore, a 19-mer antisense phosphorothioate ODN (5'-CAGCCATGGTCATCCTCCC) (SEQ ID NO: 15)

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